DOCKET NO.: CELG-0119 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Vikram Khetani, et al.

Serial No.: 09/283,645 **Group Art Unit:** 1625

Filing Date: April 1, 1999 **Examiner:** C. Chang

For: Processes and Intermediates for Resolving Piperidyl Acetamide Stereoisomers

DATE OF DEPOSIT: 3/11/02

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231.

Richard D. Watkins

TYPED NAME: Richard D. Watkins
REGISTRATION NO.: 50,993

Assistant Commissioner for Patents
Washington DC 20231

TRANSMITTAL OF APPEAL BRIEF

1. Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on December 10, 2001 .

2. **STATUS OF APPLICANT**

☒ Applicant(s) has previously claimed small entity status under 37 C.F.R. §1.27 .

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 C.F.R. §1.27 as:

☐ an Independent Inventor

☐ a Small Business Concern

☐ a Nonprofit Organization.

3. **EXTENSION OF TERM**

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136 apply.

☒ Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)-(d)) for the total number of months checked below:

	SMALL ENTITY		NOT SMALL ENTITY	
■ ONE MONTH EXTENSION OF TIME	$55	$55.00	$110	$
☐ TWO MONTH EXTENSION OF TIME	$200	$	$400	$
☐ THREE MONTH EXTENSION OF TIME	$460	$	$920	$
☐ FOUR MONTH EXTENSION OF TIME	$720	$	$1440	$
☐ FIVE MONTH EXTENSION OF TIME	$980	$	$1960	$
☐ LESS ANY EXTENSION FEE ALREADY PAID	minus	($)	minus	($)
■ APPEAL BRIEF	$160	$160.00	$320	$
TOTAL FEE DUE		$215.00		

4. **FEE PAYMENT**

☒ A check in the amount of $ **215.00** is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

☐ Please charge my Deposit Account No. 23-3050 in the amount of $___. A duplicate of this transmittal is attached.

5. **FEE DEFICIENCY**

☒ If any additional extension and/or fee is required, this is a request therefor and to charge Deposit Account No. 23-3050.

☒ If any additional fee for claims is required, charge Deposit Account No. 23-3050.

6. ☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

Date: 3/11/02

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In re application of:

Khetani, et al

Serial No.: 09/283,645 Group Art Unit: 1625

Filed: April 1, 1999 Examiner: Chang, C.

For: PROCESSES AND INTERMEDIATES FOR RESOLVING PIPERADYL ACETAMIDE STEREOISOMERS

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Washington, D.C. 20231

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 1.192

Applicants appeal the Final Rejection dated August 8, 2001, in connection with the above-identified application. An Advisory Action dated October 25, 2001, reaffirmed the rejections in the Final Rejection. A Notice of Appeal with appropriate fees was filed on December 10, 2001.

I. Real Party in Interest

The real party in interest in the above-identified patent application is Celgene Corporation, a corporation of Delaware, which is the assignee of Vikram Khetani, Yalin Luo, Sowmianarayanan Ramaswamy.

II. Related Appeals and Interferences

There are no other appeals or interferences known to Appellant, Appellant's legal representative, or the assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

III. Status of Claims

The present application was filed with original claims 1-14. Claims 9 and 14 were cancelled during prosecution and claim 15 was added. Claims 1-8, 10-13, and 15 are on appeal, and appear in Appendix A.

IV. Status of Amendments

No amendments were filed after the final rejection.

V. Summary of the Invention

The appealed claims are directed to synthetic processes and intermediates for preparing piperidyl acetamides.

Substituted piperadines have found use in the treatment of many nervous system disorders (Specification at page 1, lines 8-9). For example, methylphenidate has been used to treat Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) (*id.* at lines 9-13).

However, many prior routes to methylphenidate and other substituted piperidines involved the preparation of racemic mixtures, which have disadvantages (*id.* at page 1, line 14 – page 2, line 2). The administration of racemic methylphenidate, for example, results in

side effects such as anorexia, weight loss, insomnia, dizziness and dysphoria (*id.* at page 2, lines 2-4).

Appellants' claimed processes produce *d-threo* piperadyl acetamide stereoisomers preferentially with respect to the *l-threo* stereoisomers. These processes generally involve reacting a mixture of *d,l-threo* piperadyl acetamide stereoisomers with an acid resolving agent in an organic solvent, thereby forming acid salts of the *d-threo* stereoisomers preferentially with respect to the *l-threo* stereoisomers. The salts thus formed can then be isolated. In certain embodiments of the invention, the *d,l-threo* piperadyl acetamide stereoisomers are prepared by reacting a pyridine with hydrogen in an alkanoic acid having 1 to about 10 carbon atoms in the presence of a catalyst to provide a mixture of *threo* and *erythro* piperadyl stereoisomers; and contacting the *erythro* stereoisomers with organic base, thereby converting said *erythro* piperadyl stereoisomers to *threo* piperadyl stereoisomers.

VI. Issues

Two issues remain for resolution in this appeal:

1. whether or not the Examiner has established that the subject matter of claims 1 and 15 is identically disclosed by Jursic, *et al., Tetrahedron: Asymmetry*, Vol. 5, No. 9, p. 1712 ("the Jursic reference"); and

2. whether or not the Examiner has established that the subject matter of claims 1-8, 10, 11, 13, and 15 would have been obvious to those of ordinary skill in the art in view of the disclosure of the Jursic reference, Berrang, *et al.* CA 97:38738 ("the Berrang abstract"), Ohashi, *et al.*, CA 104:186157 ("the Ohashi abstract") or Vanderplas,*et al.* CA 118:101538 ("the Vanderplas abstract").[1]

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[1] Although claims 1-8, 10-13, and 15 stand rejected for alleged obviousness-type double patenting in view of claims 1-9 of U.S. Patent No. 5,936,091, Appellant submits that

VII. Grouping of the Claims

Appellants believe that claims 1-8, 10-13, and 15 stand or fall together.

VIII. Arguments

A. The Jursic Reference Does Not Disclose the Claimed Methods

The Jursic reference does not anticipate claims 1 or 15 because its disclosure differs from the claimed subject matter in at least three respects: (1) the Jursic reference does not disclose the claimed "acid resolving agent"; (2) the reference does not disclose the claimed formation of a salt; and (3) the reference does not disclose any isolation of such a salt. Accordingly, the rejection for alleged anticipation in view of the Jursic reference is improper and should be withdrawn.

1. No Disclosure of the Claimed "Acid Resolving Agent"

The Examiner is mistaken with respect to her suggestion (Office Action dated January 25, 2001, page 2) that the Jursic reference is anticipatory because each of the amide-containing compounds disclosed on page 1712 thereof fall within the scope of the claim term "acid resolving agent." Although the Examiner alleges that the disclosed compounds are "acid resolving agents" because their respective amide hydrogens can, in theory, be removed, the term "acid resolving agent" does not include any and all compounds from which a hydrogen moiety can be removed. Rather, as is clear from a review of the claims, the term refers to compounds that function as acids with respect to the piperadyl acetamide stereoisomers whose use the claims require. Thus, "acids" according to the claims are not

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this rejection should be deferred pending resolution of the issues of alleged anticipation and obviousness because it would be premature for Appellants to submit a terminal disclaimer of the type solicited by the Examiner until the identity of the allowed claims has been

compounds that simply include "removable" hydrogen moieties, but, rather, compounds whose hydrogen moieties can be removed by the recited piperadyl acetamides.

Significantly, there is no reason to suspect that the piperadyl acetamides recited in the claims are sufficiently basic to remove an amide hydrogen from any of the compounds disclosed on page 1712 of the Jursic reference. Accordingly, the reference cannot be said to disclose the claimed "acid resolving agent."

The Examiner has failed to raise any genuine dispute regarding Appellants' arguments as to the absence of any anticipatory disclosure in the Jursic reference. For example, although the Examiner notes that "acids" are compounds that act as proton donors or as electron pair acceptors (Final Office Action at page 2), there is no evidence of record indicating that any of the compounds in the Jursic reference that the Examiner has cited would donate protons or accept electrons when employed in the claimed processes, or that such compounds would otherwise function as the claimed "acid resolving agents." Accordingly, the Examiner's proffered definition of the term "acid," without more, fails to demonstrate that the Jursic reference is anticipatory.

2. No Disclosure of the Claimed Salt Formation

The Examiner has failed to demonstrate that the Jursic reference discloses the claimed salt formation. In accordance with Appellants' invention, a mixture of *d,l-threo* piperidyl acetamide stereoisomers is reacted with an acid resolving agent in an organic solvent to form acid salts. Although the Examiner appears to suggest that the hydrogen-bonded complexes said to be disclosed by the Jursic reference constitute "salts" of the type recited in the claims (Final Office Action at page 2), Appellants are not aware of any definition of the term "salt" that includes hydrogen-bonded complexes, nor is there any evidence of record supporting

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established. If each of claims 1-8, 10-13, and 15 is deemed allowable, Appellants are prepared to submit a suitable terminal disclaimer.

such a definition. Thus, the alleged disclosure of salt formation in the Jursic reference cannot serve as a basis for rejection.

3. No Disclosure of the Claimed Salt Isolation

Because, as noted above, the Jursic reference does not disclose salt *formation*, the Examiner is necessarily mistaken with respect to her allegation (Final Office Action at pages 2-3) that the reference discloses salt *isolation*.

Moreover, even if such salts *were* formed, the Examiner still would be in error with respect to her allegation that the Jursic reference discloses an isolation step. The Examiner, for example, is mistaken as to her allegation that the Jursic reference includes a "chromatogram," and also as to her related suggestion that the reference somehow demonstrates that the authors conducted a chromatographic separation procedure (Final Office Action at pages 2-3). What the Jursic reference shows are NMR spectra that, as recognized in the art and acknowledged by the authors, were generated using an analytical technique that did not involve any separation of the analyzed compounds.[2]

Thus, the alleged disclosure of salt isolation in the Jursic reference cannot possibly serve as a basis for rejection of the appealed claims. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) (anticipation is established only if each and every element set forth in a claim is found in a single prior art reference).

B. The Examiner Has Not Identified Any Motivation for Combining the Respective Teachings of the Cited Reference

The Examiner has failed to identify any motivating force that would have impelled those of ordinary skill in the art to combine the respective teachings of the Jursic reference

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[2] Indeed, the Jursic reference discloses analysis of a mixture of compounds *without* separating them. *See, e.g.*, Jursic reference at page 1713 ("By adding the chiral resolving agents [to a mixture of enantiomers] the signals for all possible stereoisomers are separated and their integral ratio corresponds to the isomer ratio in the mixture.").

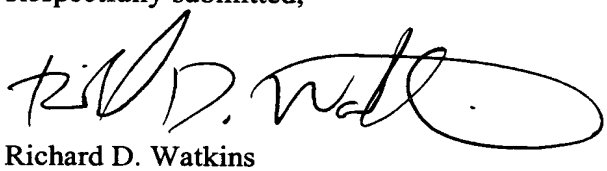
October 25, 2001, at pages 2-3), there is no reason to believe that such a disclosure would have motivated those of ordinary skill to use organic acids in their place. Indeed, the Jursic reference teaches that ***amide*** functionality is the key attribute in a resolving agent, and that the disclosed resolution techniques can tolerate the varying degrees of acidity exhibited by the disclosed class of ***amide-containing*** compounds. Although the Examiner alleges that persons of ordinary skill would have been motivated to use an organic acid by the knowledge that tartranilic acid and tartaric acid "function interchangeably" (Office Action dated August 8, 2001, at page 3), the Examiner fails to provide any evidence that such persons would have recognized these compounds to be functionally interchangeable. Thus, the Examiner's allegations of obviousness are factually unsupported.

Since there is no evidence of record indicating that those of ordinary skill would have been motivated to modify the disclosure of the Jursic reference in the manner proposed by the Examiner, the rejections for alleged obviousness are improper and should be withdrawn.

IX. Conclusion

For the foregoing reasons, the rejections of claims 1-8, 10-13, and 15 under 35 U.S.C. §§ 102(b) and 103(a) are improper and should be reversed

Respectfully submitted,



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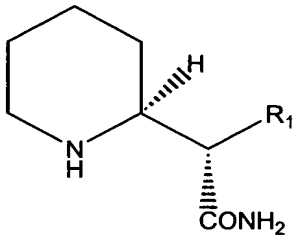
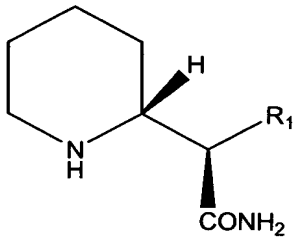
APPENDIX "A" TO APPELLANT'S BRIEF

1. A synthetic process for preferentially forming *d-threo* acid salts of *d-threo* piperadyl acetamide stereoisomers with respect to *l-threo* piperadyl acetamide stereoisomers comprising the steps of providing a mixture of said *d,l-threo* piperadyl acetamide stereoisomers having formulas:



l-threo



d-threo

wherein R_1 is aryl having about 6 to about 28 carbon atoms; and

reacting said stereoisomers with an acid resolving agent in an organic solvent.

2. The process of claim 1 wherein R_1 phenyl.

3. The process of claim 1 wherein said solvent comprises an alcohol, an alkyl alkanoate a ketone, or an ether.

4. The process of claim 1 wherein said solvent is an alkyl alcohol having 1 to about 5 carbon atoms.

5. The process of claim 1 wherein said alkyl alcohol is isopropanol.

6. The process of claim 1 wherein said acid resolving agent is a derivative of D-tartaric acid.

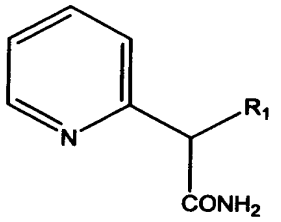
7. The process of claim 1 wherein said acid resolving agent is a tartaric acid derivative having formula $HO_2CCH[OC(O)R_3]CH[OC(O)R_3]CO_2H$ wherein each R_3, independently, is aryl having 6 to about 28 carbon atoms or aralkyl having 7 to about 28 carbon atoms.

8. The process of claim 7 wherein R_3 is aralkyl having 7 to about 28 carbon atoms.

10. The process of claim 1 further comprising reacting said *d-threo* acid salts with aqueous base to form said *d-threo* piperidine acetamide.

11. The process of claim 10 further comprising reacting said *d-threo* piperidine acetamide with an alcohol having 1 to about 5 carbon atoms in the presence of acid to form a *d-threo* piperidine acetate.

12. The process of claim 1 wherein said *d,l-threo* piperadyl acetamide stereois mers are prepared by reacting a pyridine having formula:



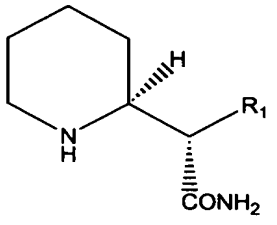
with hydrogen in an alkanoic acid having 1 to about 10 carbon atoms in the presence of a catalyst to provide a mixture of *threo* and *erythro* piperadyl stereoisomers; and

contacting said *erythro* stereoisomers with organic base, thereby converting said *erythro* piperadyl stereoisomers to *threo* piperadyl stereoisomers.

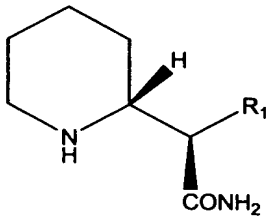
13. The product of the process of claim 1.

15. A synthetic process for preferentially forming *d-threo* acid salts of *d-threo* piperadyl acetamide stereoisomers with respect to *l-threo* piperadyl acetamide stereoisomers comprising the steps of:

providing a mixture of said *d,l-threo* piperadyl acetamide stereoisomers having formulas:



l-threo



d-threo

wherein R_1 is aryl having about 6 to about 28 carbon atoms;

reacting said stereoisomers with an acid resolving agent in an organic solvent, thereby forming acid salts; and

isolating said acid salts.